REMARKS

Reconsideration of this Application is respectfully requested.

Amendments to the Specification

Applicant has made several amendments to the specification in response to objections by the Examiner. No new matter has been added.

Status of the claims

Upon entry of the foregoing amendments, claims 1-7, 9-22, and 24-54 are pending in the application. Claims 8 and 23 are canceled and Claims 9-18 and 30-45 are withdrawn. Thus, claims 1-7, 19-22, 24-29, and 46-54 are under prosecution. Claims 1-4, 6, 19-22, 24, 25, and 53 are amended herein. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendments and the following remarks, applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Restriction Requirement

Applicants appreciate the Examiner's statement that the election of species requirement set for the in section 9 of the Office Action mailed June 5, 2003 is withdrawn.

Specification Objections

Applicants have amended the specification to comply with the sequence disclosure requirement on pages 7, 24, 25, 27, and 34. Listings of sequences appearing in Figures 2 and 3 are appropriately identified in amendments to the Brief Descriptions of the Drawings on page 7 of the specification.

Trademarks have been properly demarcated on pages 48 and 70 of the specification by amendment herein.

The ATCC deposit accession number has been added to the disclosure on pages 21, 31, and 46 of the specification by amendment herein.

The spelling of Clontech on page 76 of the specification has been corrected by amendment herein.

Claims Objections

Objections to claims 4,5, 20-22, 24 have been addressed by amendments to the claims herein.

Claims Rejections under 35 U.S.C. §112, First Paragraph

Claims 21, 22, and 54 stand rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one of skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As evidenced by the submitted receipt, Applicants have submitted the claimed plasmid to the ATCC and therefore request that the rejection be removed.

Claims Rejections under 35 U.S.C. §112, Second Paragraph

Claims 1-7, 19, 25-29, and 50-53 stand rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

As recommended by the Examiner, Applicants have amended claim 1 to recite a positive process step of "providing a DNA single chain antibody construct library, wherein said DNA single chain antibody construct library comprises a plurality of single chain antibody expression constructs" (step d). In accordance with the Examiner's recommendation, Applicants have further amended claim 1 to recite "wherein detection of expression of said detectable gene identifies a host cell containing a DNA construct encoding a single chain monoclonal antibody fusion reagent that binds the transcription associated biomolecule within said host cell". Thus, Applicants contend that amended claim 1 is definite under U.S.C. §112, Second Paragraph. Claims 2-7 depend from claim 1, and therefore incorporate the amendment to claim 1. Applicants therefore respectfully request that the rejection to claims 1-7 be removed.

The Examiner also asserts that claim 25 is indefinite for reciting "said transcription associated biomolecule" and "said fusion reagent" without antecedent basis. Applicants have amended claim 25 to instead recite "a transcription associated biomolecule" in step (a) and "said chimeric peptide" in step (e)."A transcription associated biomolecule" is fully supported by the specification and does not require antecedent basis. In step (e), "said chimieric peptide" refers to "a chimeric peptide that binds said antigenic portion" in step (c). Thus, Applicants assert that claim 25 as amended is definite, and respectfully request that the rejection of claim 25 be removed.

The Examiner has rejected claims 50, 51, and 53 as indefinite for reciting "the screening method according to claim 24" and claim 52 for reciting "the screening method of claim 51", where claim 24 is not drawn to a method. Applicants have amended claims 50, 51, and 53 to change their dependency to claim 25, which is drawn to a screening method. Claim 52 depends from claim 51, now amended to depend from a method claim. Applicants assert that the claims as amended are definite, and therefore respectfully request that the rejection be removed.

The Examiner has not provided a basis for the rejection of claim 19 under 35 U.S.C. 112, second paragraph. Applicants therefore respectfully request that the rejection be removed.

Rejections under 35 U.S.C. §102 (b)

The Examiner has rejected claim 19 as anticipated under 102(b) by Baron et al. (Gene 1992 114: 239-243), as evidenced by Apt et al. (Mol Gen. Genet. 1996 252: 572-9). Applicants disagree that Baron et al. disclose a vector for the construction and screening of a single chain monoclonal antibody fusion reagent as set forth in claim 19. Nevertheless, to expedite prosecution, claim 19 has been amended to recite a shuttle expression vector comprising at least one nuclear localization signal encoding sequence, at least one constitutive transactivation domain encoding sequence, and a zeocin selectable marker gene.

The Examiner has also rejected claim 24 as anticipated under 102(b) by U.S. Patent number 5,283,173 or Fields et al. (). As detailed in the section on , above, Applicants have amended claim 24 to more

Rejections under 35 U.S.C. §103(a)

Claims 1, 20, 25, 27-29, and 47-49

The Examiner has rejected claims 1, 20, 25, 27-29, and 47-49 under §103(a) as being obvious over U.S. Patent number 5,283,173 in view of Hoeffler et al (Meeting Abstract, Tahoe, CA: February 1994, J. Cell Biochem, 1994, Suppl. 18D, 190). Applicants disagree that these references meet all the requirements for obviousness under §103(a). In particular, Applicants assert that the combined references 1) are not enabling, and 2) do not provide motivation to a skilled practitioner to practice the invention as set forth in claim 1. Further, Applicants assert that 3) a person of average skill in the art at the time the invention was made would not have a reasonable expectation of success in practicing the invention of claim 1.

The disclosure of Hoeffler relates several ideas for "isolating immunoglobulin variable domains with high affinity for desired antigens". It goes on to say: "The variable domains that have been targeted to date have been directed towards signal-responsive transcriptional regulatory factors of the Cyclic AMP Response

Element Binding protein/Activating Transcription Factor (CREB/ATF) family." This statement does not indicate that the variable domains have been identified, isolated, or characterized, it merely states that they "targeted" for investigation. After this statement the abstract continues:

> "The *goal* of these *initial* studies has been to *target* fusion molecules containing the antigen-recognizing variable domain as a chimeric protein to endogenous DNA-bound transcriptional factors that are unstimulated under basal conditions. (emphasis added)

In particular, the disclosure of Hoeffler merely lays out in very broad strokes what might be done. No general or specific criteria for constructs, methods, or conditions for selecting variable domains that recognize transcription associated biomolecules are provided.

For example, Hoeffler et al. give no guidance as to how to generate single chain antibody – transcriptional activator chimeric protein libraries, in which the single chain antibody that is fused to a transcriptional activation domain can bind a transcription associated biomolecule with a cell.

Moreover, the art at the time of filing does not provide a rationale or strategy for overcoming inherent difficulties in using the yeast two hybrid system for screening for proteins that interact with transcription associated biomolecules. U.S. Patent No. 5,283,173 (Fields et al.) provides methods of screening for proteins that interact with a protein or peptide of interest. Applicants respectfully disagree with the Examiner's statement that '173 teaches that the protein of interest in the yeast two hybrid system is an antibody. Columns 1 and 2 of '173 discuss the prior art. Column 7, lines 42-44 state: "This system can be used to select genetically for proteins that interact with a known protein, provided the gene encoding the known protein is available." Applicants respectfully assert that this does not constitute a disclosure of the (amended) claim 1 limitation:

> (d) providing a DNA single chain antibody construct library, wherein said DNA single chain antibody construct library comprises a plurality of single chain antibody expression constructs, wherein each of said plurality of expression constructs comprises a nucleic acid fragment that codes for a single chain antibody fused to a nucleic acid that codes for a trans-activation peptide, wherein said single chain antibody is expressed in a bio-active form that may bind to said antigenic portion;

At the time the invention was made, antibody screening procedures could be efficiently performed in many reliable and quantitative formats, such as, for example, ELISA. No rationale was evident for using the more complex yeast two hybrid procedure, involving several cloning and transformation steps as well as cell culture screening, to obtain an antibody to a protein such as a transcription associated biomolecule.

In addition to providing no disclosure of, or rationale for, the use of the two hybrid method for antibody screening, it also notable that the '173 patent does *not* provide any disclosure or even suggestion of screening for proteins that interact with transcription associated biomolecules, as recited in claim 1.

Screening for binding of a molecule (such as an antibody) to transcription associated molecules would be expected to lead to ambiguities when the assay readout itself was transcription. In practicing the yeast two hybrid system, the protein or peptide of interest used as "bait" is fused to a DNA binding domain (DBD) that binds a transcription regulatory region upstream of a reporter gene. Another protein or peptide (the "prey") is fused to a transcriptional activation domain, such that when the two constructs (bait and prey) are expressed in the same cell, the binding of bait and prey results in the transcriptional activation domain coming into proximity with the DBD at the transcriptional regulatory region and stimulating transcription of the reporter gene.

The use of a transcription associated biomolecule, or a portion thereof, as bait in a two hybrid screen is counter to the conceptual design of the assay since the assumption of one skilled in the art of transcriptional regulation would have been that the results of such a screen are likely to be uninterpretable. This could reasonably be assumed to be due to any one or more of: 1) The transcription associated biomolecule (TAB)used as bait could bind DNA gene regulatory sequences that are the same as or different from the DNA recognition sequence of the DBD used in the fusion protein that also encodes the "bait". In these instances, the binding affinities of the TAB could compete with or enhance those of the DBD, providing a result that did not reflect antibody recognition of the TAB, but rather intrinsic characteristics of the TAB. 2) The transcription associated biomolecule (TAB) could itself stimulate or repress transcription of the reporter gene based on its gene regulatory effects, again leading to a reporter gene readout not indicative of antibody affinity for the TAB. 3) The TAB could recruit other transcriptional associated biomolecules to the promoter region of the reporter gene which could have either positive or negative gene regulatory effects, also resulting in reporter gene expression levels not indicative of antibody affinity for the TAB. 4) The TAB could compete with the binding or block the activity of other transcriptional associated biomolecules to the promoter region of the reporter gene, which could have positive or negative gene regulatory effects.

In short, using an assay that relies on reconstituting a transcription factor to obtain antibodies to other transcription factors would pose inherent difficulties, since the assay was intended to assess protein-protein interaction, but the results could instead reflect inherent properties of the transcription associated biomolecule under investigation. In contrast, the isolation, screening, and characterization of specific antibodies using well-established and more direct techniques was well known. The abstract of Hoeffler et al. does not address these issues, nor indicate that the yeast two hybrid system had been successfully utilized for the identification of antibodies recognizing transcription associated biomolecules.

Thus, the disclosure of Fields and Song (the '173 patent) and the abstract of Hoeffler et al. do not independently or in combination provide a reasonable rationale, motivation, or expectation of success for

screening for single chain antibody fusion reagents capable of binding a transcription associated biomolecule within a host cell, as recited in claim 1. Applicants therefore assert that claim 1 is not nonobvious with respect to '173 and Hoeffler et al., and respectfully request that the rejection be removed.

Claim 20, drawn to a kit for screen a DNA construct library for a single chain antibody fusion reagent, has been rejected by the Examiner as obvious over Fields et al. ('173) in view of Hoeffler et al. Applicants disagree that Fields et al. ('173) and Hoeffler et al. disclose all the limitations of claim 20. For example, neither the '173 patent nor the Hoeffler et al. abstract disclose:

> (a) a first expression vector comprised of (i) a first nucleic acid fragment that codes for a DNA binding domain peptide of a transcription activator that binds a DNA regulatory sequence binding site, and (ii) a second nucleic acid fragment that codes for an antigenic portion of a transcription associated biomolecule, wherein said first and said second fragments are in the same translation reading frame, whereby said first expression vector encodes a chimeric DNA-binding domain/transcriptional associated biomolecule;

Thus claim 20 is not obvious with respect to the cited references, and applicants respectfully request that the rejection be withdrawn.

The Examiner has rejected claim 25 as obvious over Fields et al. ('173) in view of Hoeffler et al. Applicants disagree for the same reasons presented for claim 1,above. In addition, neither Fields ('173) nor Hoeffler et al. disclose a screening method using an expression vector comprising, in part, a nucleic acid segment that codes for an antigenic portion of a transcription associated biomolecule that is not endogenous to the host cell, as required by claim 25. Thus, neither Fields et al. ('173) nor Hoeffler et al., alone or in combination, disclose all the limitations of claim 25. Thus, claim 25 is nonobvious with respect to the cited references, and Applicants respectfully request that the rejection be removed.

Applicants assume the rejection of claims 25, 27-29, and 47-49, which depend from claim 1, are predicated on the rejection of claim 1. Applicants traverse these rejections on the same grounds as the rejection for claim 1 is traversed, namely, the '173 patent does not disclose use of the two hybrid system to screen antibodies nor does it disclose a transcription associated biomolecule as a protein of interest that can be fused to a DNA binding domain. Hoeffler does not make up for these deficiencies, providing no enabling disclosure for isolating single chain antibody fusion reagents capable of binding a transcription associated biomolecule within a host cell. Further, the references do not provide either motivation or a reasonable expectation of success for practicing the invention as set forth in claim 1. Applicants therefore respectfully request that the rejections of claims 25, 27-29, and 47-49 be removed.

Claims 2-7, 26, and 46

The Examiner has rejected claims 2-7, 26, and 46 as unpatentable under §103(a) over U.S. Patent No. 5,283,173 ('173) in view of Hoeffler et al. (J. Cell biochem.1994; 190:422) and further in view of Biocca et al. (Trends Cell Biol. 1995 June 5; 5: 248-252).

Applicants traverse this rejection, and maintain that '173, Hoeffler et al., and Biocca et al. do not disclose all the limitations of claims 2-7, 26, and 46.

As set forth above, applicants disagree with the Examiner's assertion that '173 and Hoeffler et al. teach the limitations of claims 1, 20, 25, 27-29, and 47-49. Applicants also assert that there is no motivation provided by the references to practice the invention as claimed, and no reasonable expectation of success in practicing the invention at the time the invention was made.

Further, with regard to claim 2, Applicants assert that there is no motivation to combine Biocca et al. with Hoeffler and the '173 patent. Biocca et al. describes the use of antibodies expressed within a cell to be targeted to particular molecules at particular sites within the cell, for example, to neutralize the effects of the target molecules. In contrast, the yeast two hybrid system uses a transcriptional assay in which the bait and prey constructs are not, targeted to particular cellular compartments. There is therefore no motivation to combine Biocca with '173 or Hoeffler et al.

With regard to claim 3, none of '173, Hoeffler et al., and Biocca et al. disclose a construct comprising a single chain antibody expression construct as detailed in claim 2, comprising an intracellular targeting signal peptide, in which the trans-activation domain has been deleted.

With regard to claims 4-7, applicants assert that there is no motivation to combine a reference on "intracellular immunization" using antibodies expressed within a cell, with the screens of the present invention, direct to isolating antibodies with specificity to the named proteins.

Claim 26 recites the screening method of claim 1, in which the antigenic portion of the transcription associated biomolecule is not endogenous to the host cell. Claim 46 recites the kit of claim 20, in which the antigenic portion of the transcription associated biomolecule is not endogenous to the host cell. Applicants assert that the methods of using intracellular antibodies described in Biocca et al., for inactivating pathogenic proteins, are in no way analogous to the screening of single chain antibodies of the present invention, used to investigate the function of transcription associated biomolecules. Applicants contend that the references cited would not motivate one of average skill in the art of transcriptional regulation to use the yeast two hybrid system to screen for single chain antibodies to transcription associated biomolecules that are not endogenous to the host cell.

Because '173, Hoeffler et al., and Biocca et al. do not disclose all the limitations of claims 2-7, 26, and 46, and because motivation for combining the references is lacking, Applicants contend that the claims are nonobvious under under §103(a) and respectfully request that the rejection be removed.

Nonstatutory Double Patenting

Applicants will address the provisional double patenting rejection when patentable subject matter has been established.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Respectfully submitted,

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